REMARKS

By the present amendment, claims 1, 3, 8, 11, 17 18 and 19 have been amended and claims 2 and 4 have been deleted, rendering claims 1, 3, and 5-23 pending in the present application. The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiner's objections. Applicant reserves the right to pursue any of the deleted subject matter in a further divisional, continuation or continuation-in-part application.

The Official Action dated September 3, 2002 has been carefully considered. It is believed that the amended claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Specification

The specification has been amended at page 1 in order to update the status of the parent application.

Information Disclosure Statement

We are enclosing herewith an Information Disclosure Statement (IDS). The IDS contains the same references that were in the IDS filed January 23, 2001. The IDS has been updated in order to include the names of dates of the patent documents. This Information Disclosure Statement is being filed after the mailing date of a first Office Action; therefore, the government fee of $180.00 as provided in 37 CFR 1.17(p) is included in our cheque No. .

35 U.S.C. §112, second paragraph

The Examiner has objected to the claims under 35 U.S.C. §112, second paragraph. Claim 1 has been objected to in view of the phrase "chimera". We assume the Examiner was referring to the term "chimeric" as the term "chimera" does not appear in claim 1. In any event, the term "chimeric nucleic acid sequence" would be readily understood to one of skill in the art to be a sequence that is comprised of the first, second and third nucleic acid sequences as set forth in the claims. In response to the Examiner's question, both the sequence and the molecule are chimeric as they relate to the same entity. No further clarification is necessary.

The Examiner has asked "in a)-1) and 2), what are the nucleic acid sequences operatively linked to". We respectfully submit that the claim is clear that the first nucleic sequence is operatively linked to the second nucleic acid sequence which is operatively linked to the third nucleic acid sequence. No further clarification is necessary.

The Examiner also comments that claim 1 is an incomplete method because the final step "obtaining seed" does not produce the desired product. We respectfully disagree as the method is a method for producing chymosin *in plant seed* and the final step of obtaining seed that contains chymosin would satisfy the preamble of the claim.

The Examiner has objected to claim 3 as having an improper claim dependency. In response, claim 3 has been amended in order to depend from claim 1.

The Examiner has objected to claim 4 and Applicant has adopted the Examiner's proposed language in amended claim 1.

The Examiner has asked that the term "signal" be inserted after "PR-S" in claim 8 which Applicant has done by the present amendment.

The Examiner has requested that the term "obtainable" be changed to "obtained" in claim 11 which Applicant has done by the present amendment.

The Examiner comments that the phrase "codon usage" lacks antecedent basis in claim 12. We respectfully disagree as the term "codon usage" is not preceded by the article "the" or "said" and therefore no antecedent basis is necessary. The phrase is being used for the first time in claim 12.

In claim 13, the terms in parenthesis are the Latin names for the various types of plants that are claimed.

The Examiner has asked that claim 17 be clarified. We respectfully submit that step (e) is clear that one would be selecting plants that are produced in the earlier steps of the claim.

The Examiner comments that the phrase "said seed" is unclear in claim 18. In response, claim 18 has been amended to specify that the seed would be the seed that is obtained in step (c) of claim 1.

The Examiner comments that claims 19-23 are dependent on claim 1 which is a method of producing whereas claims 19-23 are methods of purification. We respectfully disagree as these claims depend from claim 18 which adds a further

step to the method of claim 1 that specifies that the chymosin is isolated from the seed.

The Examiner comments that the phrase "fraction" in claim 19 is unclear. We respectfully disagree as the phrase "or a fraction thereof" would be clear to one of skill in the art to mean any fraction obtained from the crushed plant seed.

In view of the foregoing, we respectfully request that all of the objections to the claims under 35 U.S.C. §112, second paragraph be withdrawn.

35 U.S.C. §112, first paragraph

The Examiner has objected to claims 18-23 under 35 U.S.C. §112, first paragraph, alleging that the specification is only enabling for isolating chymosin from (1) an aqueous fraction and (2) from *Brassica napis* seed. We respectfully disagree with the Examiner for the reasons that follow.

(1) Regarding the objection to any fraction, Applicant has amended claim 19 in order to define the fraction as an "aqueous fraction" which overcomes this objection.

(2) Regarding the objection to any seed, the Examiner states that the specification is only enabling for the isolation of chymosin from *Brassica napis* seed. We submit that the inventors have produced chymosin using the method of the invention in several other types of plant seeds including safflower, flax and *Arabidopsis*. In this regard, we are enclosing a Declaration under 37 CFR §1.132 executed by inventor Dr. Gijs van Rooijen which demonstrates the production of chymosin in safflower, flax and *Arabidopsis* and wherein the seed contains at least 0.5% (w/w) chymosin as is

required by the claims. Accordingly, we respectfully submit that the application is enabling for the production of at least 0.5% (w/w) chymosin in any plant seed.

In view of the foregoing, we respectfully request that the objection to the claims under 35 USC §112, first paragraph, be withdrawn.

35 U.S.C. §102

The Examiner has objected to Claims 1-7, 11 and 13-19 as being anticipated by Willmitzer et al. (WO 92/01042). We respectfully disagree with the Examiner for the reasons that follow.

By the present amendment the claims have been amended to specify that the first nucleic acid sequence capable of regulating transcription is a seed specific promoter and at least 0.5% (w/w) of the total seed protein is chymosin. Support for this amendment can be found throughout the disclosure for example page 3, line 24, page 7, line 13 and Example 4 and in Table 1.

In order to anticipate the claims, Willmitzer et al. must provide a disclosure of each and every element of the claims. Willmitzer clearly does not disclose the production of a transgenic plant wherein at least 0.5% of the total seed protein is chymosin. Willmitzer only achieves the production of 0.1% - 0.5% chymosin of the total soluble protein (see: page 15, line 14). In *Scripps Clinic & Research Foundation v. Genentech, Inc.* (927 F.2d 1565, 18 USPQ 2d 1001 Fed Cir:1991), the Court held that in order for there to be anticipation, the prior art must place the invention in the possession of the public by providing an enabling disclosure of how to make and use the claimed subject matter. Willmitzer clearly does not enable the production of

chymosin in plant seed wherein at least 0.5% of the total seed protein is chymosin. Consequently, Willmitzer cannot be said to anticipate the claims of the invention.

In view of the foregoing, we respectfully request that the objections to the claims under 35 U.S.C. §102 be withdrawn.

35 U.S.C. §103

The Examiner has also objected to claims 1-8, 10, 11 and 13-23 under 35 U.S.C. §103(a) as being unpatentable over Willmitzer et al. either alone or in combination with Applicant's admitted prior art or Adang et al. We respectfully disagree with the Examiner for the reasons that follow.

As stated above, Willmitzer et al. does not disclose the expression of chymosin in seed wherein at least 0.5% of the total seed protein is chymosin. Willmitzer is generally concerned with the preparation of enzymes in plants and is not specifically concerned with the improved methods for the production of chymosin. Willmitzer discloses methods for the expression of various enzymes in various plant parts including leafs, roots, stem segments and other plant parts. Example 1, and prophetic Examples 3 and 4 of Willmitzer teach the expression of chymosin in plant leaves and tubers. The construct employed by Willmitzer in Example 1 involves the use of a 35-S CaMV promoter (i.e. an art recognized strong constitutive promoter) to drive expression. Importantly, using this promoter results in a yield of chymosin of only 0.1-0.5% of the total soluble protein (Page 15, line 14). Applicant points out that total soluble protein represents only a fraction of the total protein, namely that fraction of all proteins which is soluble. In contrast the present inventors have unexpectedly found that expression of chymosin can be significantly enhanced or improved by expressing the chymosin in seed using a seed specific promoter. This results in chymosin

expression levels exceeding 0.5% of total seed protein. Applicant notes that expression levels exceeding 0.5% ot total seed protein are required in order to produce chymosin in plant seeds in a commercially viable fashion.

Applicant respectfully submits that a person of ordinary skill in the art having considered Willmitzer and desiring to attain improved expression levels of chymosin in plant cells would not find sufficient guidance in Willmitzer to achieve the method of present invention for the following reasons. Firstly, while Willmitzer may suggest the expression of enzymes in seed, Willmitzer mentions a range of other plant parts including leafs, roots, stems, tubers and other plant parts are equally (if not more) desirable plant parts for expression. Willmitzer provides no guidance or suggestion that preparing chymosin in seed would improve the yield. Thus the Willmitzer disclosure provides no motivation to select seed as a preferring plant part with a reasonable expectation of success (i.e. achieving the desirable significantly improved expression levels). Secondly, while seed-specific promoters are suggested by Willmitzer as one possibility, a person of ordinary skill in the art having read the Willmitzer disclosure would not be compelled to select a seed specific promoter from all possible promoters and expect that chymosin expression would be enhanced. Thirdly the chymosin expression levels attained by Willmitzer, using a strong constitutive promoter, are substantially lower than those attained by the present inventors. As mentioned previously, Willmitzer only achieves chymosin levels of 0.1% to 0.5% of the total soluble protein. There is nothing in Willmitzer that would lead a person of ordinary skill in the art desiring to attain improved chymosin expression levels to attempt expression of chymosin in plant seed under the control of a seed specific promoter with a reasonable expectation of success of achieving chymosin expression levels in excess of 0.5% of total protein.

In summary, the present inventors have unexpectedly found that expression levels of chymosin in excess of 0.5% of total cellular protein are attainable by expressing chymosin under the control of a seed-specific promoter in plant seeds. The invention is an improvement over Willmitzer as a significant enhancement in chymosin yield is obtained. Willmitzer provides absolutely no guidance or suggestion on how one of skill in the art would improve chymosin production. Therefore Willmitzer cannot be said to render the claims obvious. The deficiencies in Willmitzer are not remedied by Applicant's prior art or by Adang.

In view of the foregoing, we respectfully request that the objection to the claims under 35 U.S.C. §103(b) be withdrawn.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

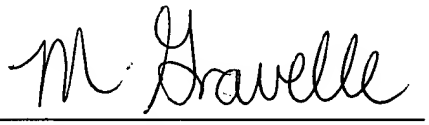
The Commissioner is hereby authorized to charge any additional fees that are required to our Deposit Account No. 02–2095.

In view of the foregoing, we submit that the application is in order for allowance and an early indication to that effect would be greatly appreciated. Should the Examiner

like to discuss the matter, she is kindly requested to contact Micheline Gravelle at 416-957-1682 at her convenience.

Respectfully submitted,

Gijs van Rooijen, Richard Glenn Keon,
Yin Shen and Joseph Boothe



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph on page 1, lines 3-5 has been amended as follows:

--This application is a continuation-in-part application of United States serial no. 09/378,696, filed August 23, 1999 (now abandoned), which is incorporated herein by reference in its entirety.--

In the Claims:

Claims 1, 3, 8, 11, 17, 18 and 19 have been amended as follows:

1. (Amended) A method for the production of chymosin in a plant seed comprising:

a) introducing into a plant cell a chimeric nucleic acid sequence molecule comprising in the 5' to 3' direction of transcription:

1) a [first nucleic acid sequence] seed-specific promoter capable of regulating transcription in said plant cell operatively linked to;

2) a second nucleic acid sequence encoding a chymosin polypeptide operatively linked to;

3) a third nucleic acid sequence capable of terminating transcription in said plant cell;

b) growing said plant cell into a mature plant capable of setting seed wherein said seed contains chymosin; and

c) obtaining seed from the mature plant wherein [said seed contains chymosin] the seed contains at least 0.5% (w/w) chymosin.

3. (Amended) The method according to claim [3] 1 wherein said seed-specific promoter is a phaseolin promoter.

8. (Amended) The method according to claim 7 wherein the plant signal sequence is a tobacco PR-S signal sequence.

11. (Amended) The method according to claim 1 wherein the chymosin is a mammalian chymosin [obtainable] obtained from a bovine, sheep or goat source.

17. (Amended) A method for the production of plant seeds containing at least 0.5% (w/w) chymosin in the total seed protein comprising:

(a) introducing into each of at least two plant cells a chimeric nucleic acid sequence molecule comprising in the 5' to 3' direction of transcription:

1) a [first nucleic acid sequence] seed-specific promoter capable of regulating transcription in said plant cell operatively linked to;

2) a second nucleic acid sequence encoding a chymosin polypeptide operatively linked to;

3) a third nucleic acid sequence capable of terminating transcription in said plant cell;

(b) growing each plant cell into a mature plant capable of setting seed;

(c) obtaining seed from each mature plant;

(d) detecting the levels of chymosin in the seed of each plant obtained in step (c) or in the seed of a plant generated from the seed of a plant obtained in step (c); and

(e) selecting plants that contain at least 0.5% (w/w) chymosin in the total seed protein.

18. (Amended) A method according to claim 1 further comprising (d) isolating said chymosin from said seed obtained in step (c).

19. (Amended) A method according to claim 18 wherein (d) isolating said chymosin from said seed comprises:

(i) crushing the plant seed to obtain crushed plant seed;

(ii) contacting the crushed plant seed or an aqueous fraction thereof with a protein binding resin; and

(iii) recovering chymosin from the protein binding resin.

Claims 2 and 4 have been deleted.